CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-726/S-006

ADMINISTRATIVE DOCUMENTS

Patents and Trademarks Department

Femara® (letrozole tablets)

Patent Information

Authors:	Michael Lee, Robert A. Miranda
Document type:	
Document status:	Final
Release date:	June 6, 2000
Number of pages:	2

Patent information

The U.S. patents covering Femara® (letrozole tablets, CGS 20267) are as follows:

1. Patent Number: 4,978,672
   Patent Expiration Date: December 18, 2007
   Claims: compound, pharmaceutical composition, use
   Patent Owner: Novartis Pharmaceuticals Corporation

2. Patent Number: 5,352,795 and 5,473,078
   Patent Expiration Date: October 4, 2011
   Claims: process of manufacture
   Patent Owner: Novartis Pharmaceuticals Corporation

EXCLUSIVITY SUMMARY for NDA # 20-726 SUPPL #006
Trade Name Femara Tablets Generic Name letrozole
Applicant Name Novartis Pharmaceuticals Corporation HFD- 150

Approval Date 1-10-01

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review-only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

   d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-726 Femara

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__/ NO /__X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 025_____

Investigation #2, Study # 102_____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /__/	NO /__X_/
Investigation #2	YES /__/	NO /_X__/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /__X_/

Investigation #2 YES /___/ NO /__X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # 025

Investigation #_2_, Study # 102

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #( ) YES /_X__/ ! NO /___/ Explain: _____

_____

_____

Investigation #2

IND #( ) YES /_X_/ ! NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

/S/

Ann Staten
Signature of Preparer

12-12-00
Date

Title: Project Manager

/S/

Signature of Office of Division Director

1/2/2001
Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

FDA Links Tracking Links Check Lists Searches Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) View Word Document

NDA Number:	020726	**Trade Name:**	FEMARA (LETROZOLE) ORAL TABLETS 2.5MG
Supplement Number:	006	**Generic Name:**	LETROZOLE
Supplement Type:	SE1	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	ADVANCED BREAST CANCER IN POSTMENOPAUSAL WOMEN
Action Date:	7/12/00		

Indication # 1 First-line treatment of postmenopausal women with advanced metastatic breast cancer
Label Adequacy: Does Not Apply
Forumulation Needed: NO NEW FORMULATION is needed
Comments (if any): Waiver granted on July 7, 2000.

Lower Range	Upper Range	Status	Date
Adult	Adult	Waived	

Comments: Waived on 7-7-00. Does not apply

This page was last edited on 12/12/00

/S/ 12/12/00

Signature Date

CC: Orig NDA 20-726
DIV FILE

Femara® (letrozole tablets)
SNDA 20-726

NOVARTIS CERTIFICATION IN COMPLIANCE WITH THE GENERIC DRUG ENFORCEMENT ACT OF 1992

Novartis Pharmaceuticals Corporation certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

7/5/00
Date

Robert A. Miranda
Associate Director
Drug Regulatory Affairs

Femara® (letrozole tablets)
SNDA 20-726

Item 19. Other

Financial Disclosure

Table of contents

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

1. FDA Forms

FDA Forms 3454 and 3455 are attached as applicable

2. Overview

2.1. Process used to collect information retrospectively

- Letters were sent out to all investigators requesting financial disclosure information
- A follow up letter was sent to investigators if no reply was received after four weeks and an additional letter four weeks later if necessary
- At study close out and/or as part of retrospective collection the investigators were told to update Novartis for 1 year from LPLV (last patient last visit) at their site if any change
- retrospective collection of financial disclosure information (for studies on-going as of February 2, 1999)

2.2. Methods used to minimize bias

- independent data monitoring via Novartis or CRO
- multiple investigators used in the studies
- double-blind active controlled trials used

2.3. Description of Spreadsheets

- shows principal investigator, subinvestigators, children & spouses (if applicable)
- shows forms received
- shows whether there was something to disclose
- shows if investigator refused to reply

2.4. Summary of Findings

Only one investigator had financial information to disclose in Femara study No. 025 (at center M1836Y). The principal investigator( )reported that( )had received grant money, honoraria and consulting fees either directly or indirectly from Novartis.

3. Spreadsheets

The spreadsheets or site certification forms are attached and organized by study:

- Study No. 025
- Study No. 102

4. Individual Disclosure Forms

The individual disclosure forms containing information to disclose are attached as required. Only one investigator, Dr( )(Study 025) was included.

5. Attachments:

- FDA Form 3454
- FDA Form 3455
- Spreadsheet for Study 025 (US)
- Spreadsheet for Study 025 (non-US)
- Certification forms for Study 102
- Disclosure form containing information to disclose for Dr.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attached list	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
David Parkinson, MD	V.P., Clinical Research and Development
FIRM/ORGANIZATION: Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936	
SIGNATURE: for Margaret Dugan	DATE: June 26, 2000

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Created by Electronic Document Services/USDHHS: (301) 443-2454 EF

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning Dr. [redacted] (*Name of clinical investigator*) who participated as a clinical investigator in the submitted study Femara Study P025 (*Name of clinical study*), is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
for David Parkinson, MD	V.P. Clinical Research and Development
FIRM/ORGANIZATION: Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936	
SIGNATURE: Margaret Dugan	DATE: June 26, 2000

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3455 (3/99) Created by Electronic Document Services/USDHHS: (301) EF

Femara Protocol 25 US Financial Disclosure

Center Number	Principal Investigator	Study Facility	City	State	Form Submitted	Investigator not submitting form	Information to disclose	Investigator to disclose	Remarks:
M1388L	AIGOTTI	HEALTH ADVANCE INSTITUTE	SOUTH BEND	IN					CANCELLED PER SIF DATED 7/29/97
M1389P	ALDEN M	GRAND VIEW HOSPITAL	SELLERSVILLE	PA	YES		NO		
M1390I	ALLGOOD J	ESCONDIDO HEMATOLOGY ONCOLOGY MEDICAL CENTER	ESCONDIDO	CA	YES		NO		
M1391M	BALCUEVA E		SAGINAW	MI	YES		NO		
M1392Q	BARNES L	HOLT KROCK CLINIC	FORT SMITH	AR	NO	BARNES L			Did not participate.
M1393U	BERNSTEIN J	SCRIPPS MEMORIAL HOSPITAL ONCOLOGY RESEARCH PROGRAM	LA JOLLA	CA	NO	UGORETZ R	NO		
M1394Y	BERRY	REX CANCER CENTER	RALEIGH	NC					Did not participate in study.

Femara Protocol 25 US Financial Disclosure

Center Number	Principal Investigator	Study Facility	City	State	Form Submitted	Investigator not submitting form	Information to disclose	Investigator to disclose	Remarks:
M1395C	BIERMANN	THOMAS JEFFERSON	PHILADELPHIA	PA					Did not
		UNIVERSITY							participate in
		HOSPITAL							study.
M1396G	BITRAN	LUTHERAN GENERAL	PARK RIDGE	IL	NO	BRUETMAN D	NO		
		CANCER CARE				DEVINE S			
		CENTER				MILLER JB			
		DIVISION OF				MILNER LS			
		HEMATOLOGY				PAIK PC			
		ONCOLOGY				ROSE CG			
						STONE LA			
M1397K	BLACHLY R	NEA CLINIC	JONESBORO	AR	NO	BICE CD	NO		
M1398O	BLAYNEY DW	WILSHIRE	POMONA	CA	YES		NO		
		ONCOLOGY MEDICAL							
		GROUP							
		ROBERT AND							
		BEVERLY LEWIS							
		CANCER CENTER							
M1399S	BORDELON	GREEN CLINIC	RUSTIN	LA					CANCELLED PER
									SIF DATED
									7/14/97
M1400J	BROTHERTON TW	DANVILLE	DANVILLE	VA	NO	JOHNSON DE			
		HEMATOLOGY &							
		ONCOLOGY INC							
M1401N	BROWN R	ONCOLOGY	SARASOTA	FL	YES		NO		
		HEMATOLOGY							
		CONSULTANTS							
M1402R	CAGGIANO V	SUTTER CANCER CTR	SACRAMENTO	CA	NO	CAGGIANO V			

Femara Protocol 25 US Financial Disclosure

Center Number	Principal Investigator	Study Facility	City	State	Form Submitted	Investigator not submitting form	Information to disclose	Investigator to disclose	Remarks:
M1403V	CAMPOS L	ONCOLOGY	HOUSTON	TX	NO	MIRO QUESADA M			
		CONSULTANTS				MANNER CE			
						HOLOYE PY			
						SANFORD DB			
						WARGO MR			
						SPENCER JA			
M1404Z	CARTWRIGHT T	OCALA ONCOLOGY	OCALA	FL	NO	CARTWRIGHT T			
		CENTER							
M1405D	CERNAIANU	STATEN ISLAND	STATEN	NY					
		UNIVERSITY	ISLAND						
		HOSPITAL							
M1406H	ASBURY R	INTERLAKES	ROCHESTER	NY	YES		NO		DR. ASBURY HAS
	CHANG A	ONCOLOGY							REPLACED DR.
		HEMATOLOGY							CHANG AS PI
									PER FDA FORM
									1572 DATED
									5/6/99
M1407L	COSGRIFF T	DRUG RESEARCH	METAIRIE	LA					CANCELLED SIF
		SERVICES							DATED 11/10/97
M1408P	CUMMINGS F	ROGER WILLIAMS	PROVIDENCE	RI	NO	DORES G	NO		
	REGE V	MEDICAL CENTER				MILLER M			
		DEPARTMENT OF				AKERLEY W			
		MEDICINE							
		RHODE ISLAND							
		HOSPITAL							
M1409T	DENES A		ST LOUIS	MO	NO	DENES A			No patients enrolled.

Femara Protocol 25 US Financial Disclosure

Center Number	Principal Investigator	Study Facility	City	State	Form Submitted	Investigator not submitting form	Information to disclose	Investigator to disclose	Remarks:
M1411Q	DISTEFANO A	RESEARCH ACROSS AMERICA	DALLAS	TX	NO	PESKIND S RETTIG J			
M1410M	DICKMAN E	MERIDIA HILCREST CANCER CENTER	MAYFIELD HEIGHTS	OH	NO	DICKMAN E			
M1412U	DORR V	UNIVERSITY OF MISSOURI-COLUMBI A ELLIS FISCHEL CANCER CENTER	COLUMBIA	MO	NO	PERRY M FARHANGI M ANDERSON C ELWING T WILKES J			
M1413Y	FERRI	ALLEGHENY GENERAL HOSPITAL	PITTSBURGH	PA					CANCELLED PER SIF DATED 8/25/97
M1414C	FINE R	COLUMBIA PRESBYTERIAN UNIVERSITY MEDICAL CENTER DIVISION OF MEDICAL ONCOLOGY	NEW YORK	NY	NO	HESDORFFER C VAHDAT L TIERSTEN A STARON R			CFEM3450025002 8US
M1415G	FREDRIC RK		FORT WORTH	TX	YES		NO		
M1416K	FRONTIERA M	DEAN MEDICAL CENTER	MADISON	WI	NO	FRONTIERA M			
M1417O	GALLARDO R	UNIVERSITY OF TEXAS AT TYLER	TYLER	TX	YES		NO		
M1418S	HAINSWORTH J	SARA CANNON CANCER CENTER	NASHVILLE	TN	YES		NO		

Femara Protocol 25 US Financial Disclosure

Center Number	Principal Investigator	Study Facility	City	State	Form Submitted	Investigator not submitting form	Information to disclose	Investigator to disclose	Remarks:
M1419W	INHORN	CANCER CENTER OF SOUTHWEST VIRGINIA	ROANOKE	VA					CANCELLED PER SIF DATED 8/8/97
M1420P	JABBOURY K	JABBOURY FOUNDATION FOR CANCER RESEARCH	HOUSTON	TX	YES		NO		
M1421T	KALMAN LA	ONCOLOGY/HEMATOL OGY GROUP OF SOUTH FLORIDA	MIAMI	FL	NO	OREN ME			
M1422X	KUMAR		CLEARWATER	FL					CANCELLED PER SIF DATED 7/14/97
M1423B	LEMKE	SUNY- HEALTH SCIENCE CENTER	SYRACUSE	NY					CANCELLED PER SIF DATED 7/14/97
M1424E	LEWIS M	MEMORIAL REGIONAL CANCER CENTER	HOLLYWOOD	FL	NO	KREIN	NO		
M1426J	LIEBMANN J	NEW MEXICO ONCOLOGY HEMATOLOGY CONSULTANTS	ALBUQUERQUE	NM	YES		NO		
M1428N	LINEBERRY DK	SORRA RESEARCH CENTER	BIRMINGHAM	AL	NO	LINEBERRY DK MARSCH JT	NO		

Femara Protocol 25 US Financial Disclosure

Center Number	Principal Investigator	Study Facility	City	State	Form Submitted	Investigator not submitting form	Information to disclose	Investigator to disclose	Remarks:
M1427R	LIPTON A	HERSHEY MEDICAL	HERSHEY	PA	NO	LIPTON A			
		CENTER				RYBKA WB			
						HARVEY HA			
						HOPPER K			
						GAREIS M			
						DELO J			
						ALI SM			
						FARIDI AA			
M1428V	LYONS R	METHODIST PLAZA	SAN ANTONIO	TX	NO	LYONS RM			
						GUZLEY GJ			
						GOLDBERG HL			
						WASH CD			
						FIDIAS P			
						GOLDEN D			
						MCMURRAY DC			
M1429Z	MALAMUD	BETH ISRAEL	NEW YORK	NY					
		MEDICAL CENTER							
		CANCER CENTER							
M1430S	MARSH R	MD ANDERSON	ORLANDO	FL	NO	MARSH R			
		CANCER CENTER				BROWN CH			
						NYBERG DA			
						CLAIRBORNE A			
						MAMUS SW			
						ROBERTSON CO			
M1431W	MCCRACKEN JD	ONCOLOGY FOR SAN	SAN ANTONIO	TX	YES		NO		
		ANTONIO P A							
M1432A	MCCACHREN S	THOMPSON CANCER	KNOXVILLE	TN	NO	COWAN JD			
		SURVIVAL CENTER							
M1433E	MIRTSCHING	MEDICAL CITY	DALLAS	TX					CANCELLED PER
		DALLAS							SIF DATED 9/8/97

Femara Protocol 25 US Financial Disclosure

Center Number	Principal Investigator	Study Facility	City	State	Form Submitted	Investigator not submitting form	Information to disclose	Investigator to disclose	Remarks:
M1434I	MISKIN BM	PALM BEACH	WEST PALM	FL	NO	MISKIN B			CANCELLED PER
		RESEARCH CENTER	BEACH			ROWE DH			SIF DATED
						CANEDO S			3/2/98
						ZAMBRANO G			
						GARDNER R			
						THAYER KJ			
						SCHULTZ A			
						LARSEN WC			
M1435M	ODDERS RN	SOUTHEASTERN	RACINE	WI	NO	ODDERS R			
		WISCONSIN				MULLANE MP			
		REGIONAL CANCER				KIM BH			
		CENTER							
M1436Q	OROURKE M	HEMATOLOGY AND	GREENVILLE	SC	NO	OROURKE MA			
		ONCOLOGY				BROOKER R			
		ASSOCIATES				GLUCK WL			
						WALLS JD			
						GOCOCO IO			
						KING GW			
						GIGUERE JK			
						CHRISTMAN KL			
						GARNER BA			
M1437U	OSBORN DC	WESTERN	OLYMPIA	WA	NO	GORTON SJ	NO		
		WASHINGTON				KANG M			
		CANCER TREATMENT				ROBERTSON PA			
		CENTER				BROWN MK			
M1439Y	PENDERGRASS K	KANSAS CITY	KANSAS CITY	MO	YES		NO		
		INTERNAL							
		MEDICINE							

Femara Protocol 25 US Financial Disclosure

Center Number	Principal Investigator	Study Facility	City	State	Form Submitted	Investigator not submitting form	Information to disclose	Investigator to disclose	Remarks:
M1439C	PETRUSKA PJ	ST LOUIS	ST LOUIS	MO	YES		NO		
		UNIVERSITY							
		HEALTH SCIENCES							
		CENTER							
M1440V	PRUITT B	HARRINGTON	AMARILLO	TX	NO	NASH C	NO		
		REGIONAL							
		HOSPITAL							
		DON & SYBIL							
		HARRINGTON							
		CANCER CENTER							
M1441Z	RAISH R	PHYSICIANS	MT VERNON	WA	NO	ZIMMERMAN TA	NO		CANCELLED PER
		PHARMACEUTICAL							SIF DATED
		STUDY SERVICES							3/2/00
M1442D	OCONNOR B	ONCOLOGY CARE	FREDERICK	MD	YES		NO		DR GREGORY
		CONSULTANTS							RAUSCH IS
									REPLACED BY DR
									BRIAN OCONNOR
M1443H	READLING J	LOURDES HOSPITAL	BINGHAMTON	NY	YES		NO		
		REGIONAL CANCER							
		CENTER							
M1444L	SHIFTAN T	SHARP HEALTH AND	SAN DIEGO	CA	YES		NO		DR IVOR
	GUTHEIL J	SIDNEY KIMMEL							ROYSTON IS
		CANCER CENTER							REPLACED BY DR
									J GUTHEIL
									DR J GUTHEIL
									IS REPLACED BY
									DR T SHIFTAN
									PER FDA FORM
									1572 DATED
									1/3/00

Femara Protocol 25 US Financial Disclosure

Center Number	Principal Investigator	Study Facility	City	State	Form Submitted	Investigator not submitting form	Information to disclose	Investigator to disclose	Remarks:
M1445P	SAMBANDAM S	JMI CLINICAL TRIALS INC	SWANSEA	MA	NO	SAMBANDAM S			
M1446T	KROENER J	SCRIPPS CLINIC MS 312	LA JOLLA	CA	NO	ANDREY J	NO		DR ALAN SAVEN IS REPLACED BY DR JOAN KROENER CFEM3450025008 1US
M1447X	SCHWARTZBERG L	THE WEST CLINIC	MEMPHIS	TN	YES		NO		
M1448B	SENNABAUM	GULF POINTE CANCER CENTER	HUDSON	FL					CANCELLED PER SIF DATED 7/14/97
M1449F	SMITH R	SOUTH CAROLINA ONCOLOGY ASSOCIATES	COLUMBIA	SC	NO	MCELVEEN LJ ACKERMAN MA	NO		
M1450X	RAVICHANDER P	GREENVILLE MEMORIAL MEDICAL CENTER	GREENVILLE	SC	NO	HINES WB	NO		
M1451C	TCHEKMEDYIAN N	PACIFIC SHORE MEDICAL GROUP	LONG BEACH	CA	NO	LEVAN AM			
M1452G	TERPENNING M		SANTA MONICA	CA	YES		NO		CANCELLED PER SIF DATED 10/20/97
M1453K	TKACZUK K	UNIVERSITY OF MARYLAND CANCER	BALTIMORE	MD	NO	TKACZUK K			

Femara Protocol 25 US Financial Disclosure

Center Number	Principal Investigator	Study Facility	City	State	Form Submitted	Investigator not submitting form	Information to disclose	Investigator to disclose	Remarks:
M1454O	TRAVIS P	HIGHLANDS	FAYETTEVILLE	AR	NO	TRAVIS P			CANCELLED PER
		ONCOLOGY GROUP				BECK JT			SIF DATED
						HAYWARD M			11/10/97
						BRADFORD DE			
						CHERRY J			
M1455S	WADE	DECATUR MEMORIAL	DECATUR	IL					CANCELLED PER
		HOSPITAL							SIF DATED
									7/29/97
M1456W	WATERFIELD W	ST AGNES	BALTIMORE	MD	YES		NO		
		HOSPITAL							
M1457A	WEICHERT K	COMMUNITY	CINCINNATI	OH	YES		NO		
		RESEARCH							
		MANAGEMENT							
		ASSOCIATION							
		THE LINDNER							
		CLINICAL TRIAL							
		CENTER							
M1458E	WEISSMAN	CAPITAL DISTRICT	LATHAM	NY					CANCELLED PER
		HEMATOLOGY							SIF DATED
		ONCOLOGY							8/8/97
		ASSOCIATES							
M1460I	BERTRAM K	MADIGAN ARMY	TACOMA	WA	NO	SHEFFLER R	NO		DR. WILLIAMS
		MEDICAL CENTER				GAUR R			IS REPLACED AS
		HEMATOLOGY				TIMMONS J			PRINCIPAL
		ONCOLOGY SERVICE				JONES M			INVESTIGATOR
									BY DR. BERTRAM
									CFEM3460025007

Femara Protocol 25 US Financial Disclosure

Center Number	Principal Investigator	Study Facility	City	State	Form Submitted	Investigator not submitting form	Information to disclose	Investigator to disclose	Remarks:
M1460B	YANAGIHARA R	SOUTH VALLEY	GILROY	CA	NO	LEON J	NO		
		HOSPITAL CAMPUS							
M1461F	YANES B	MEDICAL ONCOLOGY	DAYTON	OH	YES		NO		
		HEMATOLOGY							
M1462J	ZIMMER M	DOCTORS CLINIC	VERO BEACH	FL	YES		NO		
		RESEARCH							
M1636Y					NO				
		CENTER				FELICE AJ			
		GEORGETOWN				HEYER DM			
		UNIVERSITY				GOLDSTEIN K			
		HOSPITAL				KRESSEL B			
						MONDZAC A			
						SMITH F			
						GINSBERG S			
						SACKS TL			
						ADELSON E			
						FEIGERT JM			
						HAYES DF			
M1463N	RODRIGUEZ R	DAMILUJI CLINIC	SAN DIEGO	CA	NO	RODRIGUEZ R			
						VAN LORN KJ			
M1464R	YUNUS F	METHODIST	MEMPHIS	TN	NO	YUNUS F			
		HOSPITAL CENTRAL				REED J			
		THE BOSTON				SPIERS K			
		CANCER GROUP				BOSTON B			
		PLLC				ROBERTS J			
M1465V	DIPILLO F	LONG ISLAND	BROOKLYN	NY	NO	ROSENTHAL CT	NO		
		COLLEGE HOSPITAL							

Femara Protocol 25 US Financial Disclosure

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M1837C	GUTHERIE	UNIVERSITY OF FLORIDA MEDICAL CENTER	JACKSONVILLE	FL					CANCELLED PER SIF DATED 4/14/98
M1516M	BADOLATO CJ	ASSOCIATED MEDICAL RESEARCH HEALTH ADVANCE INSTITUTE	MELBOURNE	FL	NO	BADOLATO CJ DELIGDISH CK KERCHER RL			
M1838G	HARRER G	BIG SKY HEALTH CARE	GREAT FALLS	MT	NO	GUTER KA	NO		
M1839K	LEVIN M	BROOKDALE UNIVERSITY HOSPITAL	BROOKLYN	NY	YES		NO		
M1819E	SCOUROS M	HOUSTON CANCER INSTITUTE	HOUSTON	TX	NO	SCOUROS MA TASHIMA CK TENNYSON KB			
M1840D	SILVERMAN P	CASE WESTERN RESERVE UNIVERSITY HOSPITALS OF CLEVELAND IRELAND CANCER CENTER	CLEVELAND	OH	YES		NO		
M1841H	WADE	DECATUR MEMORIAL HOSPITAL	DECATUR	GA					CANCELLED PER SIF DATED 1/19/98

Femara Protocol 25 US Financial Disclosure

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M1842L	WARD J	UNIVERSITY OF	SALT LAKE	UT	NO	WARD JH			
		UTAH HEALTH	CITY			HUSHNER JP			
		SCIENCES CENTER				BUYS SS			
		DIVISION OF				SAMLOWSKI WE			
		HEMATOLOGY				GLENN M			
		ONCOLOGY				CRIM J			
M1677O	CHAPMAN R	HENRY FORD	DETROIT	MI	NO	CHAPMAN R			
		HEALTH SYSTEM				WOLLNER I			
						ANDERSON J			
						BRICKER L			
						DOYLE T			
						LEONARD R			
						JANAKIRAMAN N			
						KISH J			
						OBRYAN R			
						STOLTENBERG M			
						LEHMAN D			
						YU B			
						TEJWANI S			
						PALLAS S			
						CASAS E			
						BARTHEL B			
						WONG W			
						PEARLBERG J			
						RAJEH N			
						YEE KH			
						SCHNEIDER J			
						NYSTROM JS			
						EVANS J			
						SCHMIDT C			

Femara Protocol 25 US Financial Disclosure

Center Number	Principal Investigator	Study Facility	City	State	Form Submitted	Investigator not submitting form	Information to disclose	Investigator to disclose	Remarks:
M1878S	JUBELIRER S	CAMCARE HEALTH	CHARLESTON	WV	NO	JUBELIRER SJ			
		EDUCATION &				SHAH AB			
		RESEARCH				FRAME JN			
		INSTITUTE				WILLIS H			
						WILLIAMS RF			
M1879W	MCCANN J	BAYSTATE MEDICAL	SPRINGFIELD	MA	NO	WEINREB S	NO		
		CENTER				MCKEE AL			
M1880P	RUBIN MS	FLORIDA CANCER	FORT MEYERS	FL	NO	WRIGHT BROWN V			
		SPECIALISTS							
M1901X	MODIANO MR	ARIZONA ONCOLOGY	TUCSON	AZ	NO	REBEIL JB			
		ASSOCIATES							
		ARIZONA CLINICAL							
		RESEARCH CENTER							
M1945Z	GODFREY T	LOMA LINDA	LOMA LINDA	CA	NO	GODFREY T			
		UNIVERSITY							
		MEDICAL CENTER							
M2163I	MUSS	MCHV	BURLINGTON	VT	NO	MUSS			
									2US
									NO TMF1
									DOCUMENTATION
									IN CDM
									5/3/00
M2164M	SENECAL F	ST JOSEPH	TACOMA	WA	YES		NO		
		MEDICAL							
		PAVILLION							
		NORTHWEST							
		MEDICAL							
		SPECIALTIES							

Femara Protocol 25 US Financial Disclosure

Center Number	Principal Investigator	Study Facility	City	State	Form Submitted	Investigator not submitting form	Information to disclose	Investigator to disclose	Remarks:
M2165Q	WOOD AJ	CANCER	CORPUS	TX	NO	WOOD A			
		SPECIALIST OF	CHRISIT			BARKER KG			
		SOUTH TEXAS				JANAKI LM			
						NASH ME			
						VILLAMIL A			
						STRONG DB			
						MCGLYNN LE			
						ANZALDUA R			
M2366K	GRALOW J	UNIVERSITY OF	SEATTLE	WA	NO	GRALOW J			
		WASHINGTON							
		MEDICAL SCHOOL							

Femara Protocol 25 Financial Disclosure

Center Number:	Study Number:	Principal Investigator	Study Facility:	City	Country	Form Submitted	Investigator not submitting	Information to Disclose	Investigator to disclose
20267010250001FR	FEM3450025	AUDHUY B	CENTRE	COLMAR	FRANCE	NO	BARATS JC	NO	
			HOSPITALIER				FARESS HM		
			GENERAL LOUIS				SALZE PGM		
			PASTEUR						
20267010250002FR	FEM3450025	CHOLLET P	CENTRE JEAN	CLERMONT	FRANCE	NO	CHOLLET P		
			PERRIN	FERRAND			BAILLY C		
20267010250003FR	FEM3450025	CUTULI B	CENTRE PAUL	STRASBOURG	FRANCE	NO	CUTULI B	NO	
			STRAUSS						
20267010250004FR	FEM3450025	DABAN A	CITE	POITIERS	FRANCE	NO	BOURGEOIS	NO	
			HOSPITALIÈRE LA				H		
			MILETRIE						
20267010250005FR	FEM3450025	DELOZIER T	CENTRE FRANCOIS	CAEN	FRANCE	NO	DELOZIER T	NO	
			BACLESSE				VIE B		
							OLLIVIER		
							JM		
							HARTWIG J		
							LEVY C		
							GENOT JY		
							JOLY F		
20267010250006FR	FEM3450025	FARGEOT P	CENTRE G.F.	DIJON	FRANCE	YES		NO	
			LECLERC						

Femara Protocol 25 Financial Disclosure

Center Number:	Study Number:	Principal Investigator	Study Facility:	City	Country	Form Submitted	Investigator not submitting	Information to Disclose	Investigator to disclose
20267010250007FR	FEM3460025	LE FLOCH O	HOPITAL	TOURS	FRANCE	NO	BOUGNOUX P	NO	
			BRETONNEAU				TRANQUART		
							F		
							BOITREAU L		
							REYNAUD A		
20267010250008FR	FEM3460025	LORTHOLARY A	CENTRE PAUL	ANGERS	FRANCE	NO	MAILLART	NO	
			PAPIN				P;DELVA		
							R;GAMELIN		
							E		
20267010250009FR	FEM3460025	MARTY M	HOPITAL	PARIS	FRANCE	NO	GIACCHETTI	NO	
			SAINT-LOUIS				S		
							EFTEKHARI-		
							UFOUR P		
20267010250010FR	FEM3460025	MAURIAC L	INSTITUT	BORDEAUX	FRANCE	NO	MAURIAC L		
			BERGONIE				PALUSSIERE		
							J		
							CAMPO P		
							DEBLET M		
							FLOQUET A		
20267010250011FR	FEM3460025	MIGNOT L	HOPITAL FOCH	SURESNES	FRANCE	YES		NO	
20267010250012FR	FEM3460025	MONNIER A	HOPITAL A.	MONTBELIARD	FRANCE	NO	GRANDGIRARD	NO	
			BOULLOCHE				A		
							CORBION O		
20267010250013FR	FEM3460025	MORVAN F	CENTRE	PONTOISE	FRANCE	YES		NO	
			HOSPITALIER R.						
			DUBOS						

Femara Protocol 25 Financial Disclosure

Center Number:	Study Number:	Principal Investigator	Study Facility:	City	Country	Form Submitted	Investigator not submitting	Information to Disclose	Investigator to disclose
20267010250014FR	FEM3450025	NAMER M	CENTRE ANTOINE LACASSAGNE	NICE	FRANCE	YES		NO	
20267010250015FR	FEM3450025	NETTER-PINON G	HOPITAL DE MEAUX	MEAUX	FRANCE	YES		NO	
20267010250016FR	FEM3450025	ROMIEU G	CENTRE PAUL LAMARQUE	MONTPELLIER	FRANCE	YES		NO	
20267010250019FR	FEM3450025	SERIN D	CLINIQUE SAINTE CATHERINE	AVIGNON	FRANCE	NO	SERIN D PARET M		
20267010250020FR	FEM3450025	SPIELMANN M	INSTITUT GUSTAVE ROUSSY	VILLEJUIF	FRANCE	NO	LLOMBART CUSSAC A	NO	
20267010250021FR	FEM3450025	TUBIANA MATHIEU	C.H.R.U.	LIMOGES	FRANCE	YES		NO	
20267010250022FR	FEM3450025	WEBER B	CENTRE ALEXIS VAUTRIN	VANDOEUVRE LES NANCY	FRANCE	YES		NO	
20267010250024FR	FEM3450025	NOUYRIGAT P	CLINIQUE DU CAP D'OR	LA SEYNE SUR MER	FRANCE	NO	NOUYRIGAT P		
20267010250025FR	FEM3450025	WENDLING JL	CLINIQUE DE L'ESPERANCE	HYERES	FRANCE	NO	WENDLING JL		
20267010250026FR	FEM3450025	MALAURIE E	HOPITALIER INTERCOMMUNAL DE CRETEIL	CRETEIL	FRANCE	NO	MALAURIE E MARTIN JUST M		

Femara Protocol 25 Financial Disclosure

Center Number:	Study Number:	Principal Investigator	Study Facility:	City	Country	Form Submitted	Investigator not submitting	Information to Disclose	Investigator to disclose.
20267010250027FR	FEM3450025	MAYEUR D	HOPITAL MIGNOT	LE CHESNAY	FRANCE	NO	MAYEUR D DARSE T		
20267010250028FR	FEM3450025	MARTIN C	CENTRE HOSPITALIER GENERAL	ANNECY	FRANCE	NO	MARTIN C LAPALU A GROS C		
20267010250029FR	FEM3450025	GUASTALLA JP	CENTRE LEON BERARD	LYON	FRANCE	NO	GUASTALLA JP		
20267010250030TN	FEM3450025	BEN AHMED S	CHU FERHAT HACHED	SOUSSE	TUNESIA				
20267010250002IN	FEM3450025	BAPSY PP	KIDWAI MEMORIAL INSTITUTE OF ONCOLOGY	BANGALORE	INDIA	YES		NO	
20267010250003IN	FEM3450025	MITTRA I	TATA MEMORIAL HOSPITAL	MUMBAI	INDIA	YES		NO	
20267010250001IN	FEM3450025	RAINA V	INSTITUTE ROTARY CANCER HOSPITAL	NEW DEHLI	INDIA	YES		NO	
CFEM34500250008A	FEM3450025	WETTE V	KRANKENHAUS DER BARMHERZIGEN BRUEDER	GLAN	AUSTRIA	NO	WILHELM B ILSINGER P	NO	
CFEM34500250002A	FEM3450025	STIERER M	HANUSCH KRANKENHAUS	WIEN	AUSTRIA	NO	VERDULI E	NO	
CFEM34500250001G	FEM3450025	PAVLIDIS N	UNIVERSITY OF LOANNINA	LOANNINA	GREECE	YES		NO	

Femara Protocol 25 Financial Disclosure

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20267010250002RU	FEM3450025	GARIN A	CANCER RESEARCH CENTER	MOSCOW	RUSSIA	YES		NO	
20267010250003RU	FEM3450025	GORBUNOVA V	CANCER RESEARCH CENTER	MOSCOW	RUSSIA	YES		NO	
20267010250004RU	FEM3450025	LICHNITSER M	CANCER RESEARCH CENTER	MOSCOW	RUSSIA	YES		NO	
20267010250005RU	FEM3450025	GERSHANOVICH M	PETROV INSTITUTE OF ONCOLOGY	PETERSBURG	RUSSIA	YES		NO	
20267010250004SE	FEM3450025	ALBERTSSON M	ONKOLOGISKA KLINIKEN UNIVERSITETSSJU KHUSET	LUND	SWEDEN	NO	BORGIS RKJ BOSTEDT I CWIKIEL M	NO	
20267010250002SE	FEM3450025	MALMSTROEM A	ONKOLOGISKA KLINIKEN UNIVERSITETSSJU KHUSET	LINKOEPING	SWEDEN	NO	OLALLO M	NO	
CFEM34500250002G	FEM3450025	GEORGOULIAS V	UNIVERSITY HOSPITAL OF HERAKLION	HERAKLION	GREECE	YES		NO	
CFEM34500250003G	FEM3450025	ARAVANTINOS G	GENERAL HOSPITAL OF ONCOLOGY AGIOI ANARGIRI N. KIFISSIA	ATHENS	GREECE	YES		NO	

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Femara Protocol 25 Financial Disclosure

Center Number:	Study Number:	Principal Investigator	Study Facility:	City	Country	Form Submitted	Investigator not submitting	Information to Disclose	Investigator to disclose
CFEM346002500004G	FEM3460025	KALOFONOS HP	UNIVERSITY HOSPITAL OF PATRA	PATRA	GREECE	NO	KALOFONOS HP	NO	
CFEM346002500001P	FEM3460025	KORALEWSKI P	SZPITAL SPECJALISTYCZNY IM L. RYDYGIERA	KRAKOW	POLAND	YES		NO	
CFEM346002500002P	FEM3460025	PLUZANSKA A	WOJEWODZKI SZPITAL	KRAKOW	POLAND	YES		NO	
CFEM346002500001D	FEM3460025	JAENICK FKH	UNIVERSITAETS-K RANKENHAUS EPPENDORF	HAMBURG	GERMANY	YES		NO	
CFEM346002500002D	FEM3460025	ABENHARDT W	GEMEINSCHAFTSPR AXIS PRIEMAYERSTRAS SE	MUENCHEN	GERMANY	YES		NO	
CFEM346002500003D	FEM3460025	REICHARDT P	ROBERT-ROESSLE- KLINIK - FU	BERLIN	GERMANY	YES		NO	
CFEM346002500004D	FEM3460025	BRANDTNER M	KREISKRANKENHAU S WETZLAR	WETZLAR	GERMANY	NO	BRANDTNER M	NO	
CFEM346002500005D	FEM3460025	ROHRBERG R	ONKOLOGISCHE GMEINSCHAFTSPRA XIX	HALLE	GERMANY	NO	ROHRBERG R SCHAEDLICH B		

Femara Protocol 25 Financial Disclosure

Center Number:	Study Number:	Principal Investigator	Study Facility:	City	Country	Form Submitted	Investigator not submitting	Information to Disclose	Investigator to disclose
CFEM34500250008D	FEM3450025	SCHINDLER AE	UNIVERSITAETSKL	ESSEN	GERMANY	NO	SCHINDLER		
			INIKUM ESSEN				AE		
							BARKHAUSEN		
							J		
							MUELLER RD		
CFEM34500250009D	FEM3450025	SUCHY B	GENTER STRASSE	BERLIN	GERMANY	NO	SUCHY B		
							RASENACK		
							TW		
CFEM34500250009D	FEM3450025	DENGLER REM	BAHNHOFERSTRASSE	REGENSBURG	GERMANY	YES		NO	
CFEM34500250010D	FEM3450025	VOELKL SJ	DACHAUERSTRASSE	MUENCHEN	GERMANY	YES		NO	
CFEM34500250011D	FEM3450025	HOEFFKEN K	FRIEDRICH-SCHIL	JENA	GERMANY	NO	HOEFFKEN K		
			LER-UNIVERSITY						
			JENA						
CFEM34500250012D	FEM3450025	VONMINCKWITZ G	UNIVERSITY OF	FRANKFURT	GERMANY	YES		NO	
			FRANKFURT						
CFEM34500250013D	FEM3450025	JAEGER W	UNIVERSITY OF	ERLANGEN	GERMANY	NO	JAEGER W		
			ERLANGEN						
CFEM34500250014D	FEM3450025	KATZ F	STAEDTISCHE	DARMSTADT	GERMANY	NO	KATZ F		
			KLINIKEN						
			DARMSTADT						
CFEM34500250015D	FEM3450025	WOLTER H	IM MUEHLENBACH	BONN	GERMANY	NO	WOLTER H		
			28						
CFEM34500250016D	FEM3450025	OPRI F	BENJAMIN	BERLIN	GERMANY	YES		NO	
			FRAUENKLINIK						

Femara Protocol 25 Financial Disclosure

Center Number:	Study Number:	Principal Investigator	Study Facility:	City	Country	Form Submitted	Investigator not submitting	Information to Disclose	Investigator to disclose
CFEM346002500007D	FEM3460025	MERGENTHALER HG	UNIVERSITAETSKL INIKUM CHARITE	BERLIN	GERMANY	NO	MERGENTHALER HG	NO	
CFEM346002500004P	FEM3460025	MOURA PG	HOSPITAL GERAL DE SANTO ANTONIO	PORTO	PORTUGAL	YES		NO	
CFEM346002500001C	FEM3460025	PANASCI L	JEWISH GENERAL HOSPITAL DEPARTMENT OF ONCOLOGY	MONTREAL QUEBEC	CANADA	NO	PANASCI L BATIST G MELNYCHUK D PATENAUDE F POLLAK M THIRLWELL M CRAGG L HINGS I LEGLER C BURDETTE RADOUX S LANGLEBEN A LOUTFI A MILNE C SHIBATA H TRUDEAU M WEXLER M PRCHAL J STERN D ZIDULKA J		

Femara Protocol 25 Financial Disclosure

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CFEM34500250002C	FEM3450025	LEBEL	LES CHIRURGIENS	STE FOY	CANADA	NO	LEBEL S		
			ASSOCIES	QUEBEC			POTVIN M		
			HOPITAL LAVAL				MARCEAU S		
							HOULD FS		
							KELLY L		
							TANGUAY D		
CFEM34500250004C	FEM3450025	LEGAULT SP	HOPITAL ST-LUC	MONTREAL	CANADA	YES		NO	
			ONCOLOGY CENTRE	QUEBEC					
CFEM34500250009N	FEM3450025	MAARTENSE E	R. DE GRIFWEG	DELFT	NETHERLANDS	NO	BOS MME	NO	
							TJEIM SL		
CFEM34500250005C	FEM3450025	COUTURE F	CENTRE	QUEBEC	CANADA	NO	WHITTOM R		
		WHITTOM R	HOSPITALIER				ST PIERRE		
			UNIVERSITAIRE				'PEDNEAULT		
			DE QUEBEC				L		
							GOSSELIN L		
							PINAULT S		
							FRANCOEUR		
							N		
							LANGIS P		
CFEM34500250003N	FEM3450025	DEIJK WA	RODE KRUIS	DEN HAAG	NETHERLANDS	NO	MULDER H	NO	
			ZEIKENHUIS				KEMENADE		
							JES		
CFEM34500250004N	FEM3450025	COENEN JLL	ST. SOPHIA	ZWOLLE	NETHERLANDS	NO	CARLE JS	NO	
			ZEIKENHUIS				SCHEPER		
							AGTAAMS AJ		
CFEM34500250006N	FEM3450025	NORTIER JWR	DIACONESSENHUIS	UTRECHT	NETHERLANDS	NO	NORTIER JWR		

Femara Protocol 25 Financial Disclosure

Center Number:	Study Number:	Principal Investigator	Study Facility:	City	Country	Form Submitted	Investigator not submitting	Information to Disclose	Investigator to disclose
CFEM346002500007N	FEM3460025	VANDERVEGT SG	ZIEKENHUIS OUDENRIJN	UTRECHT	NETHERLANDS	NO	MULDER LS APPELMAN PTM	NO	
CFEM346002500009N	FEM3460025	RICHEL DJ	MEDISCH SPECTRUM TWENTE	ENSCHEDE	NETHERLANDS	NO	RICHEL DJ GROB-MATERS MC		
CFEM346002500008C	FEM3460025	BLACKSTEIN M	MOUNT SINAI HOSPITAL	TORONTO ONTARIO	CANADA	YES		NO	
CFEM346002500007C	FEM3460025	GERMOND C	NORTHEASTERN ONTARIO REGIONAL CANCER CENTRE	SUDBURY ONTARIO	CANADA	NO	DORREEN M GLUCK S		
CFEM346002500008C	FEM3460025	SALTMAN D	PENTICTON REGIONAL HOSPITAL ONCOLOGY CLINIC	PENTICTON BC	CANADA	NO	SALTMAN D BRIGDEN M		
CFEM346002500001N	FEM3460025	SLEEBOOM HP	ZIEKENHUIS LEYENBURG	DEN HAAG	NETHERLANDS	NO	KIEFT GJ	NO	
CFEM346002500012N	FEM3460025	VANVEELEN H	MEDISCH CENTRUM LEEUWARDEN	LEEUWARDEN	NETHERLANDS	NO	NIJHOLT C DEGRAAF H	NO	
CFEM346002500013N	FEM3460025	BALK E.	ZIEKENHUIS DE GELDERSE VALLEI	BENNEKOM	NETHERLANDS	NO	FLORIJN E	NO	
CFEM346002500017N	FEM3460025	VANNIEROP FL	ZIEKENHUIS ST. JANSDAL	HARDERWIJK	NETHERLANDS	NO	GODDARD REW	NO	

Femara Protocol 25 Financial Disclosure

Center Number:	Study Number:	Principal Investigator	Study Facility:	City	Country	Form Submitted	Investigator not submitting	Information to Disclose	Investigator to disclose
CFEM34500250002G	FEM3450025	MANSEL RE	UNIVERSITY OF	CARDIFF	UNITED	NO	COCHRANE	NO	
			WALES COLLEGE		KINGDOM		RA		
			OF MEDICINE				ADAMSON BL		
CFEM34500250004G	FEM3450025	EVANS TRJ	BEATSON	GLASGOW	UNITED	YES		NO	
			ONCOLOGY CENTER		KINGDOM				

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INVESTIGATORS AND TRIAL CENTRE PERSONNEL FOR WHOM FINANCIAL DISCLOSURE STATEMENT REQUIRED

Trial Drug CFEM345D..... Protocol Number CFEM345 0102.....

Principal Investigator Dr S. Freestone..... Centre No. 1.....

Trial Centre Personnel	Job Title	Role in trial or relationship to Investigator as applicable
Dr. S. Freestone	Principal Investigator	Medical supervision of study and report.
Dr. M. Turner	Co- Investigator	Assist Principal Investigator in Medical aspects of trial
Dr. L. Geertsema	Co- Investigator	Assist Principal Investigator in medical aspects of trial

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CERTIFICATION/DISCLOSURE FORM

Financial Disclosure by Clinical Investigators

1. Study Name: A Single-Dose, Randomized, Open-Label, Crossover Study Comparing Generic Tamoxifen Citrate Tablets and Nolvadex® Tablets in Postmenopausal Women

2. Protocol number: CFEM345 0102

3. Investigator X Subinvestigator ☐

4. Investigator/subinvestigator Name: Dr. S. Freestone

5. Address: Inveresk Clinical Research Ltd., Origo Centre, Heriot-Watt Research Park, Riccarton, EH14 4AP, Edinburgh, Scotland

6. Telephone: +44 (0) 1875 614545 7. Fax: +44 (0) 1875 614555

8. Indicate by marking Yes or No if any of the financial interests or arrangements with Novartis of concern to FDA (and describe below) apply to you, your spouse, or dependent children:

Yes	No	
☐	■	Financial Arrangements whereby the value of the compensation could be influenced by the outcome of the study. This could include, for example, compensation that is explicitly greater for a favorable outcome, or compensation to the investigator in the form of an equity interest in the sponsor or in the form of compensation tied to sales of the product such as a royalty interest. If yes, please describe:
Yes	No	
☐	■	Significant payments of other sorts, excluding the costs of conducting the study or other clinical studies. This could include, for example, payments received by the investigator to support activities that have a monetary value greater than $25,000 (i.e. a grant to the investigator or the institution to fund ongoing research, compensation in the form of equipment, or retainers for ongoing consultation or honoraria). If yes, please describe:
Yes	No	
☐	■	A proprietary or financial interest in the test product such as a patent, trademark, copyright, or licensing agreements. If yes, please describe:
Yes	No	
☐	■	A significant equity interest in the sponsor of the study. This would include, for example, any ownership interest stock options, or other financial interest whose value cannot be easily determined through reference to public prices, or any equity interest in a publicly traded company exceeding $50,000. If yes, please describe:

or

■ I hereby certify that none of the financial interest or arrangements listed above exist for myself, my spouse, or my dependent children.

In accordance with 21 CFR Parts 54.1 to 54.8, I declare that the information provided on this form is, to the best of my knowledge and belief, true, correct, and complete. Furthermore, if my financial interests and arrangements, or those of my spouse and dependent children, change from the information provided above during the course of the study or within one year after the last patient has completed the study as specified in the protocol, I will notify(company name) promptly.

9. Name: (please print)

Signature S. Freestone

10. Date 18 Nov 1999

Novartis

CERTIFICATION/DISCLOSURE FORM

Financial Disclosure by Clinical Investigators

1. Study Name: A Single-Dose, Randomized, Open-Label, Crossover Study Comparing Generic Tamoxifen Citrate Tablets and Nolvadex® Tablets in Postmenopausal Women

2. Protocol number: CFEM345 0102

3. Investigator ☐ Subinvestigator X

4. Investigator's/subinvestigator Name: Dr. M. Turner

5. Address: Inveresk Clinical Research Ltd., Ongo Centre, Heriot-Watt Research Park, Riccarton, EH14 4AP, Edinburgh, Scotland

6. Telephone: +44 (0) 1875 614545 7. Fax: +44 (0) 1875 614565

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9. Name: (please print) M.J. Turner

Signature

10. Date 24th NOV 1999

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Novartis

CERTIFICATION/DISCLOSURE FORM

Financial Disclosure by Clinical Investigators

1. Study Name: A Single-Dose, Randomized, Open-Label, Crossover Study Comparing Generic Tamoxifen Citrate Tablets and Nolvadex® Tablets in Postmenopausal Women

2. Protocol number: CFEM345 0102

3. Investigator ☐ Subinvestigator X

4. Investigator/subinvestigator Name: Dr. L. Geertsema

5. Address: Inveresk Clinical Research Ltd., Origo Centre, Hanot-Watt Research Park, Riccarton, EH14 4AP, Edinburgh, Scotland

6. Telephone: +44 (0) 1875 614545 7. Fax: +44 (0) 1875 614555

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9. Name: (please print) DR L. GEERTSEMA

Signature

10. Date 15 Nov '99

Dr.
Study No. Femara 25

Novartis
CERTIFICATION/DISCLOSURE FORM
Financial Disclosure by Clinical Investigators

1. Study Name:

2. Protocol number:

3. Investigator ☐ Subinvestigator ☐

4. Investigator/subinvestigator Name:

5. Address:

6. Telephone: 7. Fax:

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9. Name: (please print)

Signature: [S]

10. Date: 10/22/99

19-38

Financial Disclosure Statement:

October, 1999

Dr( )has received the following payments, either directly or indirectly from Novartis.

Novartis Pharmaceuticals. Correlative Science for Protocol CGS 2026705024 (Preoperativehormone therapy) 2/98-12/99

This is a grant awarded to Dr( )through( ) to compare the molecular action of the aromatase letrozole and the antiestrogen tamoxifen in a preoperative endocrine therapy trial.

TOTAL AWARD $( )

Honoraria with respect to educational lectures, tumor boards and CME sessions on endocrine therapy for breast cancer.

TOTAL AMOUNT $( )through( )a public relations company retained by Novartis to provide physician education.

Consulting fees with respect to letrozole clinical trial results and physician education sessions

TOTAL AMOUNT $( )directly from Novartis.

This income has been reported to the IRS.

Dr( )anticipates further income from these sources and will update the FDA as requested.

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CLINICAL TEAM LEADER AND DIVISION DIRECTOR REVIEW OF SUPPLEMENTAL NDA

NDA 20726/S006

NAME OF DRUG Femara (letrozole tablets)

APPLICANT Novartis

DATE OF APPLICATION July 11, 2000

PROPOSED INDICATION

"First-line treatment of postmenopausal women with advanced breast cancer"

BACKGROUND

Femara is currently approved for "treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

The FDA requirement for approval of a new hormonal drug for initial treatment of postmenopausal women with advanced metastatic breast cancer is non-inferiority or superiority to tamoxifen for tumor response rate in randomized controlled trials comparing the new hormonal drug to tamoxifen. This is conditional that the new hormonal drug is not worse than tamoxifen for time to tumor progression (TTP) or survival. Statistical non-inferiority for TTP and survival need not be shown, but the new hormonal drug and tamoxifen must at least be similar. Survival data will usually be immature at the time of approval. A Phase 4 commitment to submit follow-up survival data is required.

Non-inferiority of the new hormonal agent to tamoxifen for TTP or survival would not be adequate for approval because tamoxifen has never been shown to have a favorable effect on TTP or survival in this patient population. Of course better survival for the new hormonal drug would be adequate for approval. Better TTP for the new hormonal drug would also be adequate for approval provided survival is similar.

CLINICAL TRIALS

One randomized controlled double-blind double dummy multinational clinical trial was conducted in 916 postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced (Stage IIIB or locoregional recurrent disease not amenable to treatment with surgery or radiation) or advanced metastatic breast cancer comparing Femara 2.5 mg orally once daily with Tamoxifen 20 mg orally once daily. The safety and efficacy data are shown in the following Tables.

Table 1 Efficacy Results per Novartis and per FDA

	Novartis			FDA		
	Femara 453 pts	Tam 454 pts	p	Femara 453 pts	Tam 454 pts	p
Response Rate						
CR	34 (8%)	13 (3%)		39 (9%)	14 (3%)	
PR	103 (23%)	79 (17%)		108 (24%)	84 (18%)	
Total	137 (30%)	92 (20%)	0.0006[1]	147 (32%)	98 (21%)	0.0003[1]
Resp Duration (mo)	17.0	16.5	Not Done	11.5	10.3	Not Done
Median TTP (mo)	9.4	6.0	0.0001[2]	9.87	6.15	0.0001[2]

[1] Chi Square Test, Two-Sided

[2] Log Rank test, Two-Sided

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Table 2 Serious AE's per FDA

Toxicity	Femara (455 pts)	Tamoxifen (455 pts)
Peripheral thromboembolic events	8 (2%)	11 (2%)
Cardiovascular events	7 (2%)	4 (1%)
Cerebrovascular events	5 (1%)	6 (2%)
Fractures	21 (5%)	18 (4%)
Endometrial cancer	0 (0%)	1 (0.2%)
Ocular toxicity	7 (2%)	5 (1%)

- Peripheral thromboembolic events included venous thrombosis, thrombophlebitis, portal vein thrombosis and pulmonary embolism.
- Cardiovascular events included angina, myocardial infarction, myocardial ischemia, and coronary heart disease.
- Cerebrovascular events included transient ischemic attacks, thrombotic or hemorrhagic strokes and development of hemiparesis.
- Fractures- 21 Femara treated patients had a total of 26 fractures compared 18 tamoxifen treated patients who had a total of 20 fractures. All, or almost all, fractures were disease-related.

Femara has a highly statistically and clinically significant advantage over tamoxifen in TTP and objective tumor response. Survival data is not yet mature, but current information indicates that Femara survival is at least as good as tamoxifen.

Femara safety is similar to tamoxifen and is acceptable for a hormonal drug in this patient population. Femara induced hypoestrogenemia has the potential for long term adverse effects on bone and the cardiovascular system. These adverse effects have not been seen in this study and the life expectancy of these patients is probably too short for them to occur. These possible adverse effects are being studied in the adjuvant setting where life expectancy is longer.

This study meets the FDA criteria for approval of a new use for a marketed drug based on results of a single study. This is a large multicenter study with results that are impressive both clinically and statistically. Results are internally consistent across prognostic subgroups.

A supportive double blind double dummy RCT in 324 postmenopausal patients with breast cancer compared Femara 2.5 mg daily and tamoxifen 20 mg daily for up to four months prior to mastectomy. Tumor response was 55% for Femara and 36% for tamoxifen (p=<0.001). Breast conserving surgery was achieved in 45% of Femara patients and 35% of tamoxifen patients (p=0.022). This study provides evidence of Femara antitumor effect in a different patient population and is supportive of the study in the proposed new indication.

The two RCTs that were the basis of approval of Femara for treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy are also supportive of Femara for the first-line indication.

On December 13, 2000 the Oncology Drugs Advisory Committee unanimously recommended approval of this SNDA.

Some labeling revisions are necessary. See labeling revised by the Femara review team.

RECOMMENDATION

This SNDA is approvable with labeling revisions. See labeling revised by the Femara review team.

/S/

Richard Pazdur, M.D.
Director Division Oncology Drugs
December 21, 2000

/S/

John R. Johnson, M.D.
Clinical Team Leader
December 21, 2000

cc NDA 20726
Division File
Staten